Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

13

Immunity to Infectious Disease

Many organisms live on or inside the bodies of others. This association is by no means always harmful to the host: for example, bacteria in the gut of ruminants digest cellulose into sugars which the mammal can then metabolize; the skin and mucous membranes of vertebrates support many normally harmless species of bacteria and fungi. Such organisms which do little or no damage to their hosts are, in an ecological sense, the most successful of parasites since they do not endanger the supply of their preferred "habitat." Many other parasites, by contrast, cause a variety of disease states, ranging from the chronic debilitation induced by blood-sucking helminths, which may remain in one host for years, to the rapidly developing infections brought about by some viruses and bacteria which may sweep through a susceptible species in weeks.

In evolutionary terms, both hosts and parasites seek to survive and propagate their kind. Vertebrates will slowly evolve, over many generations, to acquire "natural" resistance against pathogenic invaders. However, the enormous numbers and rapid generation times of most parasites, particularly microorganisms, allow them to produce new and virulent genetic variants much faster than their vertebrate hosts can change to resist them. It was probably to counter the constant threat of such "unexpected" (Chapter 1) infectious organisms that vertebrates developed an immune system, and the science of immunology has grown out of a practical desire to understand and exploit immune defense mechanisms. Evolutionary aspects of immunity are further discussed in Chapter 15; in this section we will examine what is known about immunity against infection.

13.1 IMMUNE MECHANISMS

The importance of immune mechanisms to infectious disease is demonstrated by two kinds of observations: first, that individuals who have recovered from a disease are usually immune to reinfection, and second, that people lacking some

part of their immune system are often disastrously prone to infections. The first observation has been a part of human scientific knowledge for thousands of years, while the second comes from the application of immunological ideas to modern medicine. Thus, people with hypogammaglobulinemia, abnormally low levels of gamma-globulin in their serum (Section 12.1), have very low resistance to bacterial infections although their immunity to most viruses develops normally. Patients with leukopenia (low numbers of circulating leukocytes), but with normal levels of antibody, are likewise liable to severe bacterial infections. Children lacking a thymus can cope with common bacterial infections but have deficient cell-mediated immunity (see below) and may be killed by such viruses as vaccinia and measles, or by BCG (Chapter 9) tuberculosis vaccine.

It is usual to divide immune resistance to disease into "innate" and "acquired" mechanisms (Table 13.1). Acquired immunity embraces all of the processes discussed in the rest of this book. Under "innate" resistance may be grouped a variety of usually nonspecific factors and features of the general physiology of animals which do not depend on specific immunization, but which contribute to their resistance to infectious disease. While innate immunity is perhaps not strictly part of immunology it deserves some discussion, since the mechanisms are clinically very important. Many of them act in concert with

TABLE 13.1
Principal Innate and Acquired Immune Resistance Mechanisms

Resistance mechanism	Agent
Innate	Genetic and physiological factors
	Humoral agents
	Secretions on skin and mucous membranes
	Interferon
	Natural antibody (acquired?)
	Complement
	Phagocytic cells
	Polymorphonuclear leukocytes
	Macrophages
Acquired	Antibody
	Neutralization of toxins or infective agents
	Lysis of bacteria and infected cells
	Recruitment (+antigen) of phagocytic cells
	Sensitization for opsonization
	Sensitization for K cell killing
	Cell-mediated immunity
	T cells
	Cytotoxic
	Lymphokine producing
	Activated macrophages

specific, adaptive immune processes, and in fact resistance to most diseases depends on the complex interplay of many mechanisms, both innate and acquired.

13.1.1 Innate Resistance

13.1.1.1 *"Genetic" and physiological factors*

Different species vary in their susceptibility to different parasites, for reasons which are usually unknown. Men and guinea pigs contract diphtheria, while rats are resistant. Within species there are often marked strain differences, e.g., American Indians and Negroes are much more susceptible to tuberculosis than are Caucasians. In experimental animals some genetic differences in resistance are known to be caused by differences in Ir gene inheritance (Section 11.3.7). Diet can affect resistance; starvation increases susceptibility to bacterial infections. The influence of hormones on disease resistance and immune responses has been surprisingly little studied, but must be significant, e.g., cortisone decreases phagocytosis and antibody formation.

13.1.1.2 *Humoral agents*

A variety of nonspecific agents seem to have been evolved for the specialized function of resisting potentially invasive organisms. On the skin, lactic acid in sweat and fatty acids in sebaceous secretions kill many bacteria and fungi. The mucus of respiratory and genital tracts is bacteriocidal and virucidal. An important defense mechanism against viruses is the release, within hours, of *interferon* by infected cells. This is a protein which prevents intracellular replication of the invading virus or of different viruses. The so-called "natural antibodies" are important in defense against some bacteria or viruses; by contrast with the above agents, these are *specific* immunoglobulins, usually IgM, which exist in small amounts in animals not known to have had contact with the particular pathogen studied. It is likely that they are provoked by cross-reacting antigens or by mitogens from the environment (e.g., in food, dust, or gut flora), in which case they should perhaps be classified as an acquired rather than innate resistance mechanism. Antibodies in newborn animals derived from the mother across the placenta or through the milk present a similar difficulty of classification but are often very important in conferring (passive) resistance on the young (Section 2.4).

13.1.1.3 *Phagocytic cells*

Both mononuclear and polymorphonuclear phagocytes (Section 4.2.4) are induced to congregate in inflamed sites by substances released by invading bacteria or by damaged cells. Particles that become attached to the plasma

membranes of phagocytes are engulfed and often destroyed as cytoplasmic lysosomes fuse with and discharge their hydrolytic enzymes into the phagocytic vacuoles. This kind of protection is not infallible, however, since some viruses, rickettsia, protozoa, and exceptionally hardy bacteria such as *Brucella* and *Mycobacterium tuberculosis* can survive or multiply inside phagocytic cells.

How do phagocytes discriminate between foreign particles, which they ingest, and self-components, which they normally leave alone? In the case of vertebrate phagocytes this recognition problem is often solved by allowing specific antibody to do the discriminating. Phagocytosis is greatly assisted by a group of serum substances collectively called "opsonins" (after the Greek "opsono": I prepare food for), which include some antibodies and complement (Fig. 13.1). Antibodies are often available against foreign but not self-antigens. Anything to which antibody combines will be readily phagocytized. Thus foreign material is ingested, while normal self-components are not. (It is interesting to note that *degenerating* self-components, such as old red cells, *are* often phagocytized, after first becoming coated with antibody against new antigenic determinants revealed during the degeneration process.) This relegation of self/not self decisions to antibody is conceptually satisfying, but unfortunately cannot fully explain the behavior of phagocytes, since invertebrates which have no antibody also contain phagocytic cells that do not attack their "hosts." Some other more

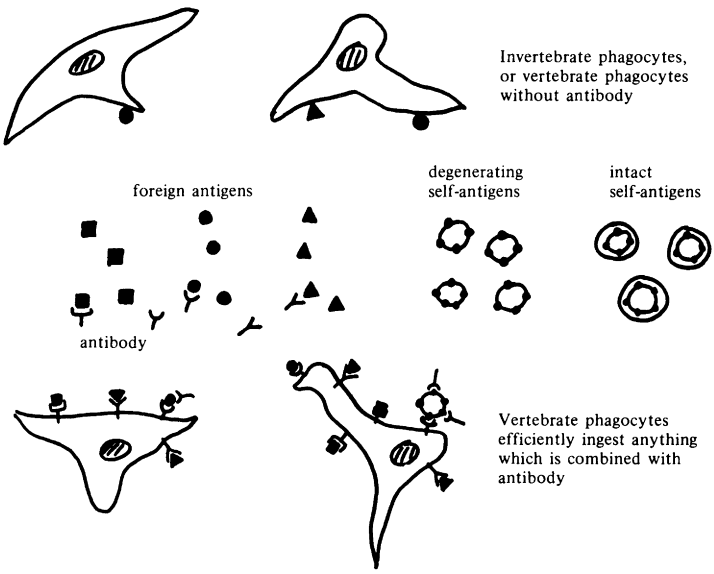

Fig. 13.1 Phagocytosis, with or without the assistance of antibody.

primitive way of distinguishing foreign objects must exist, although one would not expect this to have the same power as the vertebrate immune system to detect fine differences in chemical composition. It is likely that vertebrate phagocytes also retain some ability to ingest particles in the absence of antibody, albeit much less efficiently, although there is disagreement about this: it is difficult to prove that there is absolutely no specific antibody attached initially either to the antigen or to the surface of the phagocyte ("cytophilic" antibody, see below).

The role of phagocytic cells in immunity was the subject of violent controversy for many years. Eli Metchnikoff, a Russian biologist who in 1882 observed phagocytosis of foreign particles by scavenger cells in starfish, championed the view that this kind of mechanism alone could explain resistance to invasion by microorganisms. This was hotly contested by German workers at the Pasteur Institute in Paris, who felt that humoral factors were all important. As often happens in scientific disputes, it now seems that the truth lies between these extremes: both phagocytes and antibody are vital, and they may function cooperatively.

13.1.1.4 *Complement, and other auxilliary substances*

Complement (abbreviated C′) is a series of eleven protein components in normal serum which are involved in such defense mechanisms as opsonization, local inflammation, and lysing bacteria and cells. These proteins are normally inert, but can be activated in a complex sequential reaction analogous to the blood clotting mechanism. In (simplified) outline, the process is as follows. The first stage of activation is provoked by combination of antigen with IgM or IgG antibody, which causes a conformational change in the normal Fc structure of the immunoglobulin leading to binding of the first component of complement, C1. This bound C1 now acquires the ability to activate several molecules of the next component in the chain, which, in turn, act on the next in enzymatic fashion, one molecule triggering many in a self-amplifying cascade. The process is controlled by a series of inhibitors. At certain stages, fragments with pharmacological activities are split off the complement molecules, for example, "anaphylatoxins" which promote histamine release, and other fragments which are chemotactic for granulocytes (i.e., encourage their local accumulation). The end result of the complement cascade initiated by antibody attached to antigen on a cell surface is the activation of terminal components which can punch a microscopically visible hole in the membrane causing lysis of the cell or bacterium. In Chapters 2 and 4 we discussed how this property of complement is used in serum and plaque forming cell tests for hemolytic antibody.

Active intermediates of the complement sequence can be induced, not only by antigen–antibody complexes as in the "classical pathway" outlined above, but also by an "alternate pathway," stimulated by certain bacterial cell wall polysaccharides, such as endotoxin. *Properdin* is a 230,000 molecular weight

protein in normal serum which is involved in this alternate pathway of complement activation. *Immunoconglutinin* is an autoantibody against new antigenic determinants which are revealed when complement binds to antibody. In some species it may act to agglutinate small complexes of antigen, antibody, and complement, and promote their phagocytosis.

13.2 ACQUIRED IMMUNITY

It is worth reiterating that innate immunity may fail to provide defense against new and "unexpected" antigenic varieties of invading organisms. For this kind of rapid adaptation, vertebrates need their true immune system with its specific T cells and antibodies, produced, according to many immunologists, in almost endless diversity and by random processes. Here we will summarize the mechanisms known to be involved in acquired resistance to infectious disease before discussing those particularly relevant to various classes of parasite.

13.2.1 Antibody

The following four effects can be distinguished.

13.2.1.1 *Neutralization of toxins*

Combination near the active site of a toxin may stereochemically block its toxic activity. At a distant site, antibody may produce allosteric changes which inactivate the toxin. Toxin–antitoxin complexes are liable to phagocytosis.

13.2.1.2 *Lysis*

In the presence of complement, IgM and IgG antibodies may lyse bacteria, particularly gram-negative organisms, as discussed earlier. Some virus-infected cells are also lysed in this way.

13.2.1.3 *Recruitment of phagocytic cells*

Apart from their increased susceptibility to phagocytosis, antibody–bacteria complexes activate the complement system producing local inflammatory and chemotactic effects.

13.2.1.4 *Virus neutralization*

Antibody limits the spread and multiplication of many viruses by promoting their phagocytosis, and preventing their attachment to susceptible cells. Viruses with envelopes may be lysed by antibody plus complement. IgA antibody at mucous surfaces helps prevent access of viruses and bacteria by some mechanism which is not yet understood.

13.2.2 Cell-Mediated Immunity

Historically there has been an unwarranted preoccupation with antibody alone as the effector of immune resistance. It is easy to obtain immune serum and, after transferring it to a normal individual, to look for passively acquired immunity. However, in the early years of this century it became evident that in certain diseases like tuberculosis, antibody was not protective. In 1921, Zinsser found that a state of immunity to tuberculosis was accompanied by delayed-type hypersensitivity (Section 9.4.2). In 1942, Chase and Landsteiner showed that this immunity could be transferred to normal animals with lymphoid cells, but not with serum. Hence the term "cell-mediated immunity" (CMI). It is not an ideal name; after all, antibody is also produced by cells. However, the expression is now applied to those immunological mechanisms mediated by T cells, with or without macrophage participation, which do not involve B cells.

As discussed in Section 9.4, we can distinguish two categories of "CMI T cells": (1) those with direct complement-independent cytotoxic effects on other (target) cells such as allografts or virus-infected cells; and (2) those which, on contact with antigen, liberate lymphokines (Section 9.4.3) that have a variety of effects on other cells. This second type of cell is responsible for the local inflammation, elicited by antigen in delayed-type hypersensitivity. It is also the prime mover in the phenomenon of "macrophage activation," very important in resistance to some infections. Immunity to bacteria which multiply in normal macrophages—*Mycobacterium, Brucella, Salmonella, Listeria*—depends heavily on the increased phagocytic and bactericidal power displayed by lymphokine-activated macrophages. Resistance to some protozoan and metazoan parasites is also mediated by activated macrophages. It will be recalled from Chapter 9 that this kind of CMI reaction has two stages: the first is a *specific* combination of antigen and T cell, and the second, a variety of nonspecific effects such as recruitment of phagocytes, activation of macrophages, and blastogenesis of local lymphocytes. Cell-mediated immunity seems generally to be more important than antibody in defense against agents which multiply inside cells, such as viruses, some protozoa, and bacteria.

13.2.3 Antibody and Cells Together

Antibody and nonspecific effector cells can often work together to destroy or remove foreign cells and particles. Two mechanisms may be distinguished, both depending on the fact that the effector cell has receptors for the Fc part of IgG and sometimes for C3, a component of complement (Fig. 13.2).

13.2.3.1 *Opsonization, followed by phagocytosis*

The uptake of molecular or small particulate antigens after coating with IgG antibody depends on an initial combination with Fc receptors on the plasma

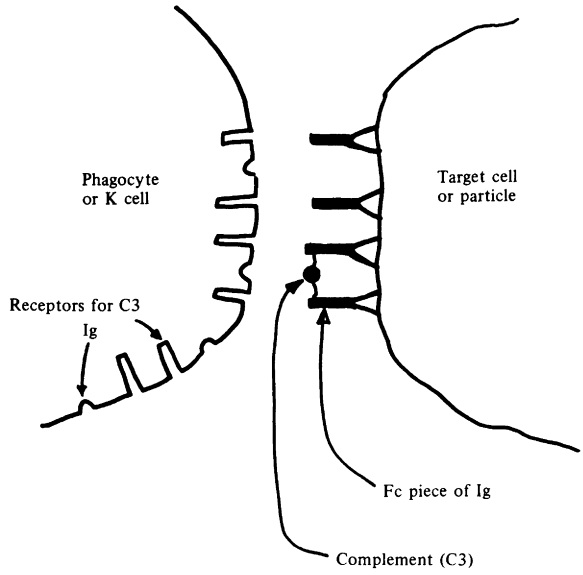

Fig. 13.2 Attachment of phagocyte or K cell to "target" particle coated with antibody, with or without complement.

membrane of the granulocyte or macrophage. Bound components of complement may assist the attchment through other receptor sites (Fig. 13.2). Phagocytic engulfment follows. (While phagocytes do not have receptors for the Fc piece of IgM antibody, they may, via their complement receptors, take up particles to which IgM antibody and complement are bound.)

13.2.3.2 *Antibody-dependent cell-mediated cytotoxicity (K cell killing)*

A class of small mononuclear cells known as K cells can also attach to the Fc part of IgG bound to target cells. There is disagreement as to whether complement may assist this union. In any case, these cells, after attachment to this cell-bound antibody, can directly destroy target cells which may be tumors, allografts, or cells infected with protozoa or microorganisms.

One might ask: "Why doesn't serum Ig inhibit this useful Fc-mediated binding of immune complexes to phagocyte and K cell surfaces?" Such inhibition can be shown *in vitro,* but it may be that *in vivo* the *multipoint* binding between an array of Fc pieces, perhaps together with complement, and their corresponding array of receptors is too strong to be inhibited by competition from monovalent Fc pieces on free IgG (Fig. 13.2). It is also possible experimentally to produce "armed macrophages," pretreated with cytophilic Fc-attached antibody molecules,

which will then bind antigen via their Fab combining sites. However, it seems unlikely that such cells are important in the body since if single Fc combinations with their receptors were normally stable, all macrophages would be saturated with a heterogeneous array of irrelevant IgG molecules.

13.3 THE IMMUNE RESPONSE TO DIFFERENT CLASSES OF INVADING ORGANISMS

Two major points should emerge from this section. First, there is a surprising lack of precise knowledge about the immune mechanisms operating against many common infectious organisms, particularly protozoa and helminths. This is partly due to the complexity of responses to living invaders and the difficulty of determining which aspects of these responses are important, and partly to the difficulty of finding experimental models which accurately represent those diseases of humans and domestic animals with which we are ultimately concerned. Second, the immune response is not always very effective. Parasitic organisms have evolved various strategies of defense against the host immune response. The small, rapidly multiplying bacteria and viruses often pass on to new hosts before the original patient has had time to destroy them with an immune response. Many viruses and protozoa prolong their survival by generating new antigenic variants as antibodies to the original types arise. By contrast the larger, slower-breeding helminths often rely on "looking" antigenically as much like their hosts as possible so as not to induce a strong immune response, or simply on being hardy enough to weather the immunological storm which they provoke. In this section we will briefly examine the kinds of immune reaction stimulated by viruses, bacteria, protozoa, and some helminths.

13.3.1 Viruses

An important first line of defense against virus infection is provided by the fixed tissue macrophages, notably the alveolar macrophages which phagocytize airborne viruses, and the phagocytic cells lining the small blood vessels of liver, bone marrow, and spleen, which dispose of particles from the blood. There is a correlation between the virulence of viruses and their ability to multiply in macrophages; for example, newborn animals are often more susceptible to virus disease than adults, and their macrophages have low virucidal powers. Antibody greatly enhances phagocytosis and thus clearance of virus from the body.

The increased susceptibility of thymus-deficient humans and of T cell-depleted (e.g., thymectomized) animals to viral infection shows that CMI is vital in recovery from primary infection, particularly against those agents like poxviruses, herpesviruses, and measles virus, which pass directly from cell to cell. It

is thought that CMI reactions protect the host in two ways: first, by destroying infected cells with cytotoxic T lymphocytes, and second, by the liberation, from sensitized T cells, of lymphokines which recruit and activate macrophages at the site of infection. A characteristic feature of many virus infections is their short incubation period, and part of the predominant importance of T cells in resistance to such infections may be attributed to the fact that the CMI response is quicker than antibody production. Interferon, produced even more rapidly, is also important. However, circulating antibody is very useful in preventing reinfection by many viruses, and in decreasing the spread of arboviruses and enteroviruses (e.g., hypogammaglobulinemics are more liable than normal to paralytic poliomyelitis). IgA at seromucous surfaces diminishes access of viruses, e.g., influenza, rhinoviruses, and coronaviruses (the last two being agents of the common cold) in respiratory passages.

While some viruses (measles, mumps, rubella, chickenpox, and smallpox) do not often undergo antigenic variation, and rely on a supply of new, nonimmune hosts for their continued propagation, others exist in a variety of antigenic forms, e.g., influenza, dengue, and poliovirus. Influenza produces recurrent human pandemics, each caused by radically new antigenic variants which emerge every few years. The disease is immunologically interesting since immunity to an older strain not only fails to protect an individual against new variants, but may even be actively harmful! This is because of the phenomenon known as "original antigenic sin." First contact with an initial or older strain, O, induces anti-O antibodies. Contact with a new strain, N, which would give anti-N antibodies in a person not previously infected with influenza, stimulates more anti-O antibodies in the O-immune individual. These antibodies are not protective against N. The mechanism is probably as described in Fig. 13.3. Because immune induction is degenerate (Chapter 11), anti-O memory cells can be induced by virus N to make anti-O antibodies. By some regulatory effect, not yet understood, this vigorous anti-O response may rapidly induce a compensating suppression which at the same time prevents the specific anti-N primary response from producing protective levels of antibody.

Another viral strategy for avoiding immune reactions is the "vertical transmission" of infectious particles from mother to offspring, the viral antigens reaching the offspring early enough to induce tolerance rather than immunity. Transmission may be via placenta, milk, the cytoplasm of the fertilized egg, or even in a DNA copy of the viral genome integrated into host chromosomes, as with some animal tumor viruses (Chapter 14). An example of a vertically transmitted virus whose study has greatly influenced immunological ideas is the agent of lymphocytic choriomeningitis in mice. This produces disease when mice are first infected as adults, but when vertically transmitted, leads to a lifelong, inapparent infection. Viral antigen is abundant, and indeed transfer of normal lymphoid cells to an infected host may provoke an immune response which is harmful to

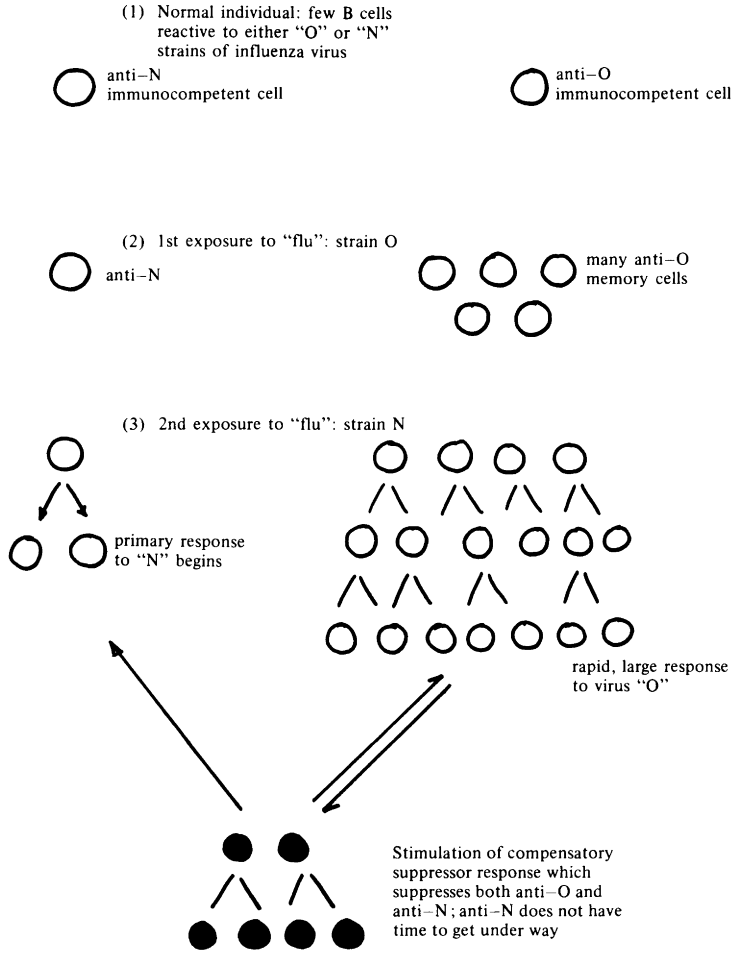

Fig. 13.3 Original antigenic sin: possible explanation.

the host. Yet the mice are essentially tolerant of the virus: they seem to regard it as part of self. This observation was one which contributed to Burnet and Fenner's early formulation of the concept of immunological tolerance.

13.3.2 Bacteria

The acquired mechanisms responsible for antibacterial immunity have been covered in Section 13.2. Antibody is thought to be particularly important in infections caused by *Streptococcus, Pneumococcus, Meningococcus,*

Pseudomonas aeruginosa, and *Haemophilus influenzae.* Antibody neutralizes toxins, and lyses some organisms if complement is available. When combined with particulate antigen, such antibody binds complement, induces local macrophage activation, and promotes phagocytosis. The existence of cell-mediated immunity may be inferred when specific skin tests of infected individuals show delayed-type hypersensitivity, as occurs in tuberculosis, brucellosis, typhoid (carrier state), syphilis, leprosy, melioidosis, and lymphogranuloma venereum. Such skin sensitivity presumably indicates that similar local reactions are occurring at foci of infection elsewhere in the body. However, it does not necessarily mean that CMI is essential for effective immunity: e.g., in *Staphylococcus aureus* and *Streptococcus pyogenes* infections, delayed hypersensitivity can be demonstrated, yet antibody confers immunity. We have already discussed the ability of some bacteria to multiply inside phagocytes, and the importance of the following pathway:

Sensitized T cell + antigen → lymphokines → macrophage activation → increased nonspecific phagocytosis and killing.

Where the parasite is sufficiently hardy to resist killing even by activated macrophages, as are many mycobacteria, chronic local antigenic stimulation may occur, encouraging the formation of granulomata. These are collections of inflammatory cells in which macrophages predominate. Their presence may have pathological consequences, but they may also serve to "wall off" the focus of infection and diminish further spread of the organism.

13.3.3 Protozoa

The pathogenic protozoa and metazoa can often successfully parasitize a single host for long periods: naturally developing immunity is obviously not very effective in these cases. This is not to deny that protective vaccines might eventually be produced (as has been done for such persistent microorganism-induced diseases as tuberculosis), but it is difficult to establish that any immune response accompanying such natural infection has clinical relevance. As a rough generalization, humoral immunity is said to be significant against protozoa in the blood, while CMI is more important against parasites in tissues. Among the mechanisms which help these organisms to resist the host immune response are: their complex life cycles, often involving many antigenically different stages; their intracellular location in many cases; possibly some release of "blocking" antigens (and see Section 14.3.4 for discussion of this effect in the resistance of tumors to immune attack); sometimes the acquisition of a "coat" of host antigens; immunosuppression of the host by the parasite in some instances. Trypanosomes and malaria organisms may also undergo repeated antigenic changes within infected hosts. These appear to be alterations in phenotypic expression of antigen rather than selection of genetic variants, and are induced by antibody in the host, implying

that immune responses against these parasites are sufficiently effective to have forced them to evolve this interesting mechanism for evading rejection.

The most important protozoan diseases of man are leishmaniasis, trypanosomiasis, and malaria. Malaria alone causes some one hundred million cases per year in tropical Africa, with a million deaths. The disease induces increased antibody formation whose clinical importance is uncertain. A beneficial increased cellular resistance is manifested by more rapid clearing of parasites and infected erythrocytes from the blood of immune people. Some resistance is transferable by cells or hyperimmune serum in experimental *Plasmodium* (malaria) infections of rats and mice. *Leishmania tropica* causes oriental sore, a disease which is accompanied by strong delayed-type hypersensitivity. In *L. donovani* infections (Kala azar) the situation is similar to malarial infections, with considerable antibody formation of unknown significance. In trypanosomiasis, evidence for useful overall protective immunity is still weak, although people and cattle in endemic areas are said to be relatively resistant to the disease.

13.3.4 Helminths

The most important helminth diseases in man are schistosomiasis and hookworm infestation. *Schistosoma* species, which are responsible for an estimated one hundred million infections in humans, are trematodes living especially in mesenteric veins. The adults acquire host antigens in their outer coats which protect them against attack, but host immune reactions are known to occur, and although the adults persist, the immature migratory schistosomula may be destroyed. CMI is thought to be more important than antibody in this resistance to reinfection. Allergic reactions to antigens of the parasite eggs contribute to the disease. There are intriguing recent reports that schistosomula may be destroyed *in vitro* by the combined action of immune serum (without complement) and eosinophils.

Hookworms are gut-dwelling, blood-sucking nematodes. They stimulate a range of immune responses, which may result in expulsion of adult worms, in a reaction which appears to involve both antibody and sensitized lymphocytes. Helminths also characteristically induce elevated levels of IgE antibody, eosinophils, and mast cells in the blood, which has led to the suggestion that local anaphylactic reactions (Section 12.2.3), with release of vasoactive amines, may contribute to the expulsion of worms.

13.4 IMMUNOLOGICAL INTERVENTION

In human and veterinary medicine, infectious diseases can be controlled in three main ways: (1) by improving hygiene, e.g., good sanitation, improved

cooking methods, destroying the mosquito vectors of malaria, wearing boots in areas where schistosome larvae would otherwise enter through the skin of exposed feet; (2) by treating established infections with drugs, such as antibiotics. Although these two modes of controlling infectious diseases are immensely important, they do have some disadvantages: hygienic improvements are not always economically feasible; drugs can only be given after infection is clinically obvious, by which time the patient may have suffered some damage; many chemotherapeutic agents have harmful side effects, which reflects the difficulty of interfering with the parasite's metabolism without harming that of the host; effective drugs are not yet available for all diseases. (3) The third method is by immunological manipulations which include (a) immunological diagnosis of present or past infection, such as testing serum antibody titers; (b) vaccination, with the aim of inducing immunity to natural infection without having to experience the actual disease; (c) immunological treatments, restricted mainly at present to administering immune antisera to, for example, suspected cases of tetanus infection.

13.4.1 Diagnostic Tests

Serum antibody tests are the simplest way of detecting prior exposure to a wide variety of infectious organisms. A rising titer with time indicates recent infection.

The most important diagnostic indication of a state of cell-mediated immunity is the skin test for delayed-type hypersensitivity. In humans there are a variety of such specific tests available, e.g., injection of mumps antigen, used to test for CMI to mumps virus, "brucellin" for brucellosis, "histoplasmin" for histoplasmosis, and a purified protein derivative of *Mycobacterium tuberculosis* for tuberculosis. *In vitro* tests on isolated lymphocytes are being increasingly explored as indicators of CMI, e.g., sensitized lymphocytes may transform into blast cells and divide when exposed to specific antigen; the normal migration of macrophages from a capillary tube is inhibited by the reaction between antigen and sensitized lymphocytes. Better standardization of CMI tests is needed. It would also be extremely helpful to have a single-cell test, analogous to the hemolytic plaque assay for antibody forming cells, for detecting sensitized T lymphocytes.

13.4.2 Vaccination

The objective of vaccination is to induce immunity in a form which prevents natural infection, and to do this without harming the patient. We have already discussed, in Chapter 2, how Jenner converted folklore into scientific fact with his investigations on the immunity to smallpox conferred by deliberate inocula-

tion of people with cowpox. We saw also how Pasteur generalized this principle: virulent organisms could be attenuated, converted into less dangerous but still immunogenic forms, by a variety of procedures including simple aging of a culture (chicken cholera bacillus), gentle heating (anthrax bacillus), or serial passage through an unusual host species (rabies). Today, a variety of attenuated viral and bacterial vaccines are in common use (Table 13.2).

In 1886, Salmon and Smith made the important discovery (with chicken cholera) that killed organisms could also provoke useful immunity. Killed vaccines are now also widely available (Table 13.2). Living vaccines usually induce better immunity than killed material, presumably because the dead organisms do not reach the same parts of the body in the same amounts as natural infectious agents. For very prolonged immunity, antigen may need to persist (Chapter 6), and the retention of small numbers of virions may underlie the common long-lasting immunity to viruses (lifelong in the case of yellow fever, for example).

To counteract the harmful effects of invading organisms it is sometimes sufficient to immunize against their toxic products (Table 13.3). In 1923, Glenny and Ramon independently discovered that mild formaldehyde treatment of diphtheria toxin could destroy its toxic activity without affecting its antigenicity. Toxin was converted into "toxoid." Tetanus toxoid was also made and first widely used in World War II when it virtually abolished tetanus infection of wounds. Today, public health immunization programs have almost eliminated a number of diseases such as polio, diphtheria, and smallpox from many communities.

TABLE 13.2
Examples of Human Vaccines

Class of vaccine	Living	Dead
Toxoids		Diphtheria Tetanus
Bacteria	BCG (=Bacillus Calmette Guerin, against tuberculosis)	Cholera Pertussis Plague Typhoid
Viruses	Measles Mumps Polio (Sabin) Smallpox Yellow fever Rubella	Influenza Rabies Polio (Salk)
Rickettsia		Typhus Rocky Mountain spotted fever

TABLE 13.3
States of Acquired Immunity

State of immunity	How acquired
Active	Natural
	Recovery from infection
	Induced
	Dead vaccines
	Toxoids
	Killed organisms
	Living attenuated organisms
Passive	Natural
	Maternal antibody
	Induced
	Artificially transferred antibody

13.4.3 Immunological Treatments

By contrast with the preventive aspirations of vaccination, treatments aim to improve the lot of patients already infected. The most common current procedure is the transfer of passive immunity with antiserum. Antibody to tetanus, diphtheria, and botulinus toxins are commonly used, human material being preferable to antisera from horses or other species because of the danger of serum sickness when large amounts or repeated doses of foreign proteins are administered (Section 12.2.4). Human gamma globulin is sometimes given to people in contact with hepatitis, smallpox, or measles. To the newborn mammal, its mother is an important natural source of passive immunity (Table 13.3), antibody being absorbed from colostrum, via the intestine of the suckling youngster, and, in some species, across the placenta.

Active immunization of infected individuals is too slow to be helpful against most viral and bacterial infections, except for rabies where this kind of treatment has been practised since Pasteur's time. The transfer of sensitized lymphoid cells instead of serum is limited by the inevitability of their rejection within weeks; as we saw in Section 10.8, antigens on lymphocytes of other members of the same species are much more immunogenic than antigens on their serum proteins. Lymphocyte transfer has, however, been used to treat chronic candidiasis and vaccinia gangrenosa. To combat broader immunodeficiencies, thymus-deficient children have received thymus transplants, and stem cell-deficient patients, bone marrow, although in this latter case graft versus host disease may cause complications (Section 10.6). "Transfer factor" is a low molecular weight, nucleic acid-containing extract of human lymphocytes which has recently been used to transfer therapeutically useful levels of cell-mediated immunity to patients with

certain fungus diseases, such as candidiasis. Its mode and specificity of action are still uncertain.

13.4.4 Possible Future Developments

Many existing vaccines could be improved. For living preparations there is often a small but real risk of reversion to virulence or of complications, such as encephalitis, which may outweigh the benefits of vaccination once the probability of contracting the natural disease is very low. There are also many important diseases against which vaccines are still either not available or not fully effective. In some of these, it seems that cell-mediated immunity would provide best protection, e.g., typhoid, leprosy, syphilis, and many diseases caused by protozoa and metazoa. In other instances, the mechanism of naturally acquired immunity is uncertain: trachoma, typhus, dengue, tick-borne encephalitis, hepatitis A and B, and chronic gonorrhea. In developing a new vaccine it is important, first of all, to seek evidence that immune resistance can be acquired. The relative importance of CMI and antibody formation should then be evaluated, and a convenient source of antigen sought which will induce immunity of the most effective kind. The site at which immunity is provoked is also often critical, for example, resistance to influenza may depend largely on IgA levels in the respiratory tract. Ideally, one wants to study "model" infection in experimental animals which mimic the natural disease of humans or domestic animals.

Vaccines are badly needed for many protozoan and helminth diseases. Three helminth vaccines are currently used, all in veterinary practice, against *Dictyocaulus viviparus* in cattle, *D. filaria* in sheep, and *Ancylostoma caninum* in dogs. All of these vaccines are irradiated immature forms of the worms. The problems of developing vaccines against well-adapted, antigenically varying organisms are immense, but it is vital that current efforts be continued and expanded because of the enormous numbers of people affected by many of these diseases.

For treatments, as opposed to vaccination, the aim is to amplify an existing immune response, or to change its character, usually from an antibody to a CMI response. Advances in chemotherapy have removed the need for immunological treatment of most bacterial diseases, and viral infections often progress too rapidly for immune intervantion to be worthwhile, but there seems to be considerable scope for immunology in many chronic protozoan, metazoan, and fungus-induced diseases, as well as in some chronic bacterial and viral infections such as leprosy and herpes. Various empirical measures can be attempted, such as injecting extracts of mycobacteria to stimulate nonspecific local immunity. This has apparently been shown to induce some resistance to *Babesia* and *Plas-*

modium, and has also been used in tumor therapy (Section 14.5). Antigenic extracts of infectious organisms can be made and tested in experimental models. However, a rational approach would seem to depend, as in so much of immunology, on a better knowledge of immune *control.* We need to know how to control the amount, the class, and the specificity of immune responses: the amount, so as to boost inadequate reactions to useful levels (and this may involve circumventing suppressor reactions); the class, so as to promote CMI rather than antibody where needed, and vice versa; and the specificity, so as to divert responses away from older variants of such organisms as influenza and the trypanosomes which rely on remaining one antigenic jump ahead of an insufficiently changeable immune response.

13.5 SUMMARY

1. Vertebrates have evolved nonspecific innate mechanisms to protect themselves against parasites. These include humoral substances and phagocytic cells.

2. Most parasites, especially microorganisms, can multiply much more rapidly than their hosts, and generate new variants against which the host species has no effective innate defense.

3. The immune response is a mechanism evolved by vertebrates to allow rapid reaction against new parasites, antigenically distinct from self.

4. Among immune resistance mechanisms are: specific antibody, cell-mediated immune responses initiated by T cells, activation of macrophages, combined effects of antibody with phagocytes or K cells.

5. Parasites have a variety of properties which help them to evade immune attack. These include:

(a) rapid transmission to new hosts (notably viruses and bacteria)

(b) intracellular multiplication and resistance to phagocytic destruction (viruses, some bacteria, and protozoa)

(c) rapid antigenic variation of parasites within one host, ahead of the immune response (trypanosomes and malaria)

(d) immunosuppression of the host (e.g., trypanosomes and malaria)

(e) periodic antigenic variation, coupled with a tendency of the host to give an ineffective secondary response against the old strain of the organism (influenza)

(f) incorporation of host antigens into the outer coat of the parasite (some protozoa and helminths)

(g) resistance to immune mechanisms (e.g., some helminths, mycobacteria)

6. Knowledge of immune mechanisms against many organisms, particu-

larly protozoa and helminths, is still very imprecise. Among the reasons for this are the following:

(a) The parasites are complex organisms, often having many different forms during their life cycle, some of which may exist outside the vertebrate host.

(b) There are often no diseases in experimental animals which mimic the diseases of importance to humans, making them difficult to study.

(c) Immune responses are often themselves complex, and it is difficult to know exactly what is happening and what facets of the responses are important.

FURTHER READING

13.1 Burnet, F. M. and White. D. O. (1972). "Natural History of Infectious Disease," 4th ed. Cambridge Univ. Press, London.

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13.4 Notkins, A. L. (ed.). (1975). "Viral Immunology and Immunopathology." Academic Press, New York.

13.5 Ogilvie, B. M. and Jones, V. E. (1973). Immunity in the parasitic relationship between helminths and hosts. *Prog. Allergy* **17,** 94.

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QUESTIONS

13.1 An animal is immunized with two unrelated kinds of bacteria, *Salmonella* and *Streptococcus*. When some of its macrophages are removed, washed, and examined *in vitro,* these cells very efficiently phagocytize either kind of bacteria, even in the absence of any immune serum. A friend of yours says this shows that macrophages do not depend on Ig opsonins for phagocytosis. You maintain that the cells have cytophilic antibody, but, to your embarrassment, this cannot be directly demonstrated by fluorescence-labeled anti-Ig staining. Devise a simple experiment to prove that these macrophages do require some kind of specific immune recognition for efficient phagocytosis of the bacteria.

13.2 As the veterinarian in a small country district you wish to confirm a suspicion, based on clinical examination, that a herd of cattle has recently been exposed to *Brucells abortus* infections, and that the infection is slowly spreading through the herd. What confirmation might you seek?

13.3 Why are people who have recovered from an attack of one strain of influenza virus sometimes less able than previously unaffected individuals to resist infection by a new strain of influenza?